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Unique Strategy for the Assembly of the Carbon Skeleton of Guanacastepene A Using an Allenic Pauson–Khand-Type Reaction

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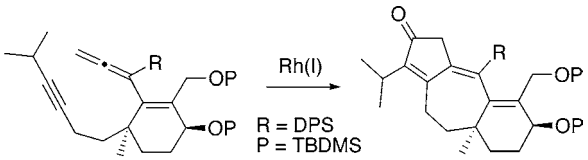
ABSTRACT



An approach to the highly functionalized tricyclic core of guanacastepene A has been developed using a rhodium(I)-catalyzed allenic Pauson–Khand reaction. This approach constitutes a conceptually novel strategy for the synthesis of this tricyclic framework, whereby the six-membered ring is formed intially followed by simultaneous formation of the five- and seven-membered rings.

Decades of complacency concerning the use of antibiotics have led to their overuse and in many cases their eventual uselessness. Bacterial resistance to multiple drugs is so commonplace that resistance to vancomycin (the antibiotic of last resort against bacteria such as *Staphylococcus aureas*) occurs for nearly 25% of the *S. aureas* infections in the United States. Interestingly, a recent account highlights the magnitude of this problem reporting on an infection from a strain of bacteria that has evolved so quickly that it has overcome the mechanistically unique antibiotic linezolid.[1] This desperate situation further underscores the necessity for continual development of new antibiotics.

Recently, unclassified endophytic fungal extracts isolated from the branch of a *Daphnopsis Americana* tree in the Guanacaste Conservation Area in Costa Rica have shown excellent activity against methicillin-resistant *S. aureas* (MRSA) and vancomycin-resistant *E. faecalis* (VREF) pathogens. The active component from these extracts was named guanacastepene A (**1**, Figure 1), a diterpene possessing a structurally unique carbon skeleton.[2] After the characterization of this compound by NMR and X-ray crystallography, a family of 14 structurally related compounds was isolated from the same fungal extract, guanacastepenes B−O.[3] Representative compounds of this family, guanacastepenes E and H are shown in Figure 1. Further biological studies established that guanacastepene A has moderate

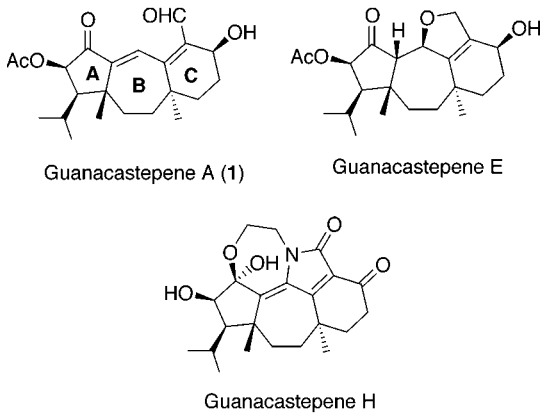


Figure 1. Guanacastepenes A, E, and H.

(1) Gonzales, R. D.; Schreckenberger, P. C.; Graham, M. B.; Kelkar, S.; DenBesten, K.; Quinn, J. P. *Lancet* **2001**, *357*, 1179.

(2) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116.

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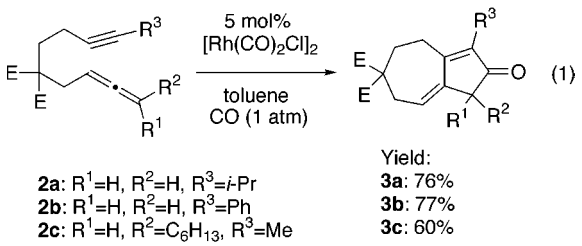
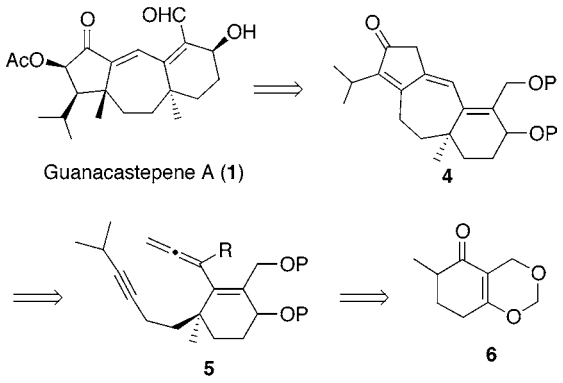
activity against gram-positive bacteria, poor activity against gram-negative bacteria, and observed hemolytic activity against human red blood cells.[4] This hemolytic property precludes the use of guanacastepene A as an antibiotic, but nonetheless guanacastepene A represents a novel lead structure for antibiotic development.

The novel carbon skeleton of guanacastepene A and its highly functionalized upper half make it a challenging and attractive synthetic target. Not surprisingly, synthetic studies have been reported by a number of groups.[5] Danishefsky and co-workers recently reported the first total synthesis of guanacastepene A,[5m,n] and shortly thereafter Snider's group reported a formal total synthesis.[5o] Both of these approaches involved a strategy that begins with the construction of the five-membered ring followed by sequential annulations of the seven- and six-membered rings, i.e., an A → AB → ABC approach. A conceptually novel route to guanacastepene A was suggested by the recent demonstration in our group showing that an intramolecular allenic Pauson−Khand reaction can be used to form seven-membered rings.[6] In this report, we were able to control the constitutional group selectivity of the reaction by simply altering the reaction conditions. In all cases examined, when rhodium biscarbonyl chloride dimer $[Rh(CO)_2Cl]_2$ was used as a catalyst to effect the allenic Pauson−Khand reaction, the cyclization occurred exclusively with the distal double bond of the allene, independent of the substitution pattern of the allene. This was the case even when the tether length was increased by one methylene unit. As can be seen in eq 1, when alkynyl allenes **2a**−**c** were subjected to 5 mol % $[Rh(CO)_2Cl]_2$, they gave only the fused bicyclic ring systems **3a**−**c**.



We believed that this novel constitutional group selectivity could be showcased in the synthesis of guanacastepene A. Retrosynthetic disassembly of guanacastepene A (**1**) leads to compound **4** containing the carbocyclic skeleton and all the necessary functionality for the conversion to guanacastepene A (Scheme 1). The 4-alkylidene cyclopentenone **4** could

Scheme 1. Retrosynthetic Analysis



in turn be obtained from alkynyl allene **5** using the allenic Pauson−Khand strategy depicted above in eq 1. This Pauson−Khand-based approach to guanacastepene A is especially attractive since the preparation of allenyne **5** could take advantage of one of many efficient and stereoselective syntheses of cyclohexenones in the literature. In addition, it is predicted that the stereocenters that are introduced after the Pauson−Khand reaction can all be set in a stereoselective manner relative to the existing stereocenters in the cyclohexenone. For these reasons, we chose cyclohexenone **6** as our desired starting material. The primary considerations for the assembly of **5** from **6** are the appropriately timed introduction of the quaternary center and the potentially sensitive allene group.

Preparation of compound **5** is ideally suited for the vinylogous ester-1,3-dicarbonyl transposition developed by Stork et al.[7] that was later modified by Smith to include a hydroxymethyl group on the cyclohexenone ring.[8] Our synthesis was initiated using Smith's enone **7** (Scheme 2).[8] Introduction of the required alkyne functionality was accomplished via an alkylation of the enolate of enone **7** using LDA and iodide **8**.[9] Unfortunately, the conversion of **7** to **11** was a low-yielding reaction (30−40%).[10] Alternative bases such as KHMDS, NaHMDS were used, in addition to varying the amount of alkynyl iodide **8**, with no measurable increase in the yield of the alkylation product **11**. The order

(3) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900.

(4) Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256.

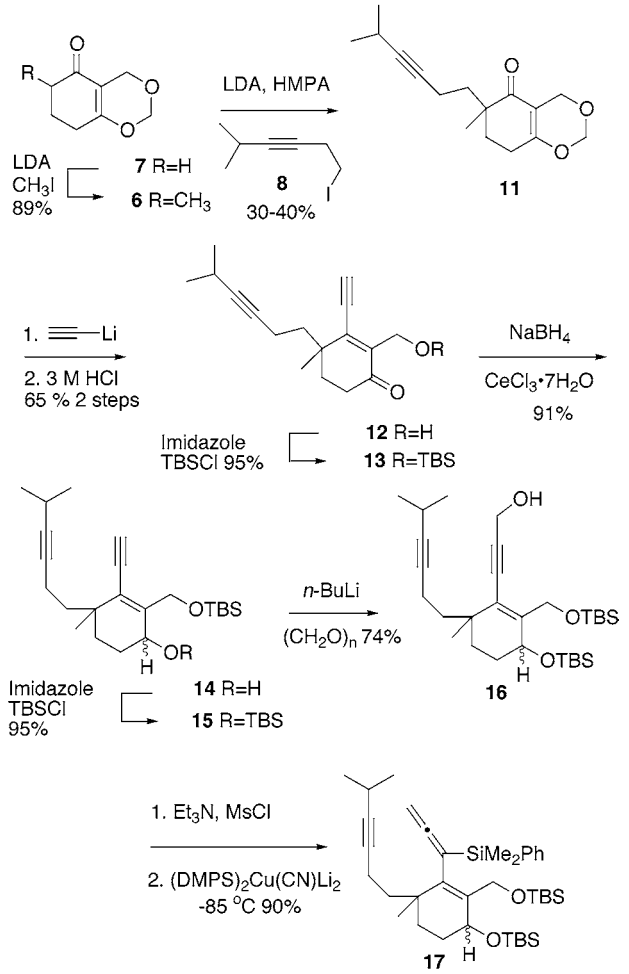
(5) (a) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399. (b) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789. (c) Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4947. (d) Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123. (e) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569. (f) Dudley, G. B.; Danishefsky, S. J.; Sukenick, G. *Tetrahedron Lett.* **2002**, *43*, 5605; Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063. (g) Mehta, G.; Umarye, J. D.; Gagliardini, V. *Tetrahedron Lett.* **2002**, *43*, 6975. (h) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063. (i) Nguyen, T. M.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 4033. (j) Nguyen, T. M.; Seifert, R. J.; Mowrey, D. R.; Lee, D. *Org. Lett.* **2002**, *4*, 3959. (k) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363. (l) Boyer, F. D.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 7469. (m) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185. (n) Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188. (o) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030. (p) Mehta, G.; Umarye, J. D.; Srinivas, K. *Tetrahedron Lett.* **2003**, *44*, 4233. (q) Xiaohui, D.; Chu, H. V.; Kwon, O. *Org. Lett.* **2003**, *5*, 1923.

(6) Brummond, K. M.; Chen, H.; Fisher, K. D.; Kerekes, A. D.; Rickards, B.; Sill, P. C.; Geib, S. J. *Org. Lett.* **2002**, *11*, 1931. Narasaka published a similar result as a single example during our investigations into the scope of this reaction. Kobayashi, T. Koga, Y.; Narasaka, K. *J. Organomet. Chem.* **2001**, *624*, 73. Another group has reported the formation of bicyclo[5.3.0]-dec-1,7-dien-9-ones from allenes via rhodium(I) catalysis. Mukai, C.; Nomura, I.; Yamanishi, K.; Hanaoka, M. *Org. Lett.* **2002**, *4*, 1755.

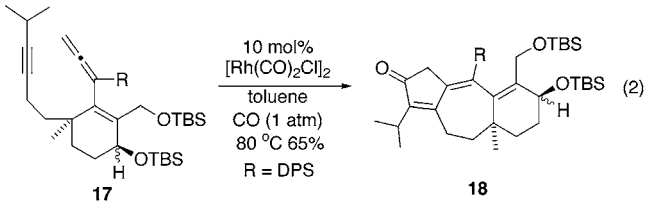
(7) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

(8) Smith, A. B., III; Dorsey, B. D.; Ohba, M.; Lupo, A. T., Jr.; Malamas, M. S. *J. Org. Chem.* **1988**, *53*, 4314.

Scheme 2. Preparation of Allenic Pauson−Khand Precursor **17**



in which the electrophiles were introduced was also reversed such that the less reactive alkynyl fragment was added first and the more reactive methyl iodide was added last. However, the overall yield for these two different approaches was similar. It was deemed advantageous to go with the former approach since compound **6** was easier to purify and more amenable to large-scale synthesis. At this point we opted to continue with this synthetic sequence in order to test the viability of the key annulation quickly. Treatment of the enone **11** with lithium acetylide ethylenediamine complex, followed by hydrolysis of the crude product with 3 M HCl, afforded enone **12** in 65% yield for two steps. (Alternatively, addition of ethynylmagnesium bromide gave only trace amounts of desired addition product.) The hydroxyl group of **12** was protected with TBSCl to give silyl ether **13** in 95% yield. The carbonyl group of **13** was then reduced using the Luche protocol to give the secondary alcohol **14** as a mixture of two diastereomers in a ratio of 3:1 (ratio measured by integration of the hydroxymethylene proton resonances in the ^{1}H NMR, and the relative stereochemistry is unknown). The two diastereomers could not be separated by column chromatography, so the mixture was taken on and the resulting allylic alcohol protected as the *tert*-butyldimethylsilyl ether to afford **15** in an 88% yield for the two steps.[11] The allene functionality was introduced via a three-step protocol developed by Fleming.[12] An allenyl silane was chosen as an additional regiocontrol element to ensure selective reaction with the distal double bond of the allene.[13] Deprotonation of the terminal alkyne **15** with *n*-BuLi at −78 °C for 30 min, followed by the addition of paraformaldehyde gives the propargylic alcohol **16** in 71% yield. Treatment of the alcohol **16** with Et_3N and MsCl yielded a mesylate, which was not purified but directly added to $(Me_2PhSi)_2Cu(CN)Li_2$ at −85 °C and allowed to react for 30 min to afford the 3,3-disubstituted allene **17** in 90% yield for two steps. With allenyne **17** in hand, it was reacted with 10% mol $[Rh(CO)_2Cl]_2$ in toluene at 80 °C to afford 4-alkylidene cyclopentenone **18** as the only Pauson−Khand reaction product in 65% yield (eq 2).



With a successful construction of the tricyclic ring system of guanacastepene A, the next step in the synthesis is to introduce the second angular methyl group. Additions have been attempted, and unfortunately we observed only the 1,2-addition product **19** (Scheme 3) when Me_2CuLi[14] and MeMgBr, CuBr·DMS, Me_3SiCl, and HMPA[15] protocols were used. Interestingly, another byproduct, fulvene **20** was identified resulting from the dehydration of the 1,2-addition

(9) Alkyl iodide **8** was prepared in three steps from 3-methyl-1-butyne (see Supporting Information). Deprotonation of 3-methyl-1-butyne with *n*-BuLi followed by the addition of ethylene oxide gives the homopropargylic alcohol **9** in 95% yield. Conversion of this alcohol to the iodide was done using a standard protocol whereby the mesylate **10** was prepared using triethylamine and methanesulfonyl chloride. The mesylate **10** was not purified but taken directly onto 1-iodo-5-methyl-3-butyne (**8**) by refluxing in acetone and sodium iodide.

(10) Studies on the dialkylation of vinylogous esters have been performed, see: (a) Foote, K. M.; John, M.; Pattenden, G. *Synlett* **2001**, *3*, 365−368. (b) Schinzer, D.; Dettmer, G.; Ruppelt, M. *J. Org. Chem.* **1988**, *53*, 3823−3828.

(11) Diastereomers were separated by HPLC for characterization purposes. (see Supporting Information)

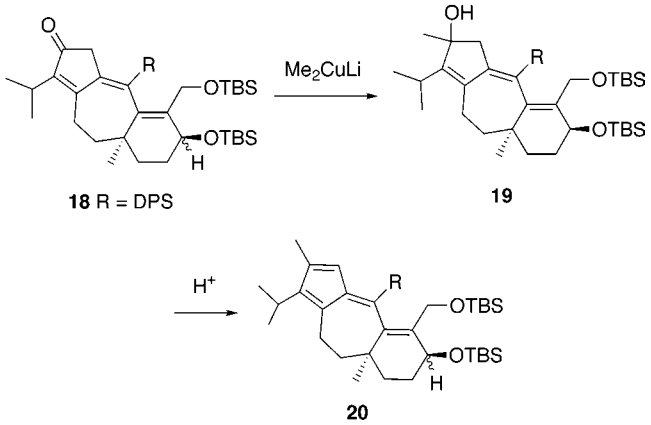
(12) Fleming, I.; Terrett, N. K. *J. Organomet. Chem.* **1984**, *264*, 99. See also: Weinreb, S. M.; Jin, J. *J. Am. Chem. Soc.* **1997**, *119*, 5773.

(13) Studies performed previously in our group have shown that Pauson−Khand reactions can be sterically directed to react with one double bond selectively. Thus, introduction of the silicon group at the proximal double bond of the allene followed by its removal at an opportune time in the synthesis seemed to be advantageous. Brummond, K. M.; Lu, J. *J. Am. Chem. Soc.* **1999**, *121*, 5087. Moreover, this additional control element may not be necessary since the Pauson−Khand ring closure of **18** (R = H) with the proximal double bond would encounter a serious interaction between the newly formed exocyclic double bond and the hydroxymethyl group on the six-membered ring.

(14) For a review, see: Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. For a mechanistic discussion, see: Vellekoop, A. S.; Smith, R. A. *J. Am. Chem. Soc.* **1994**, *116*, 2902.

(15) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *34*, 4025. Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kumwajima, I. *Tetrahedron Lett.* **1986**, *34*, 4029.

Scheme 3. 1,2-Addition vs 1,4-Addition



adduct **19**. The inability to effect the conjugate addition of a methyl group to trienone **18** was not surprising. Molecular mechanics calculations of trienone **18** using MacSpartan's conformational search (MMFF) were particularly informative.[16] Interestingly, all minimized conformers showed the dimethylphenylsilyl group on the same face as the existing angular methyl group and the cyclohexene group twisted around to the opposite face, which appears to provide very efficient blocking from the top face (Figure 2). The arrow points to the carbon of the enone in which nucleophilic addition of the methyl group must occur.

In conclusion, we have formed the carbocyclic core of guanacastepene A via an allenic Pauson−Khand-type reaction. The advantages to this novel C → CBA approach include are (1) initiation of the synthesis with the construction of a readily available cyclohexenone and (2) rapid access to the tricyclic core, which will allow for facile preparation of other members of the guanacastepene family and analogues.

(16) Methyl and *tert*-butyldimethylsilyl ethers were used in two independent calculations. Conformational analysis gave similar results, so the methyl ether depiction was used for viewing ease.

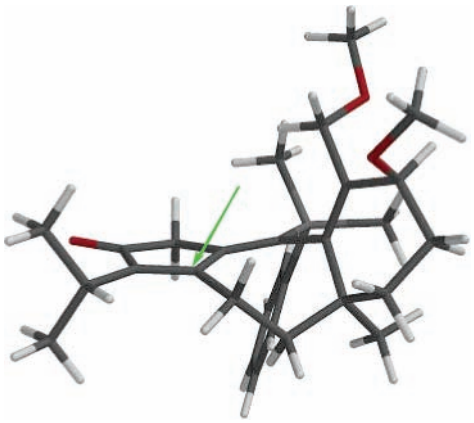


Figure 2. Conformational preference of **18**.

Acknowledgment. We thank the National Institutes of Health (GM54161) and the Johnson & Johnson Focused Giving Award for financial support of this project.

Supporting Information Available: Characterization data and full experimental procedures are provided for compounds **8** and **11**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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